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Patent Form 1/77

19 APR 2002

NEWPORT

Request for grant of a patent

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1. Your reference	P30323-/GMM/PMC/MEA		
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2. Patent Application Number (the Patent Office will fill in this part)	0208945.6		19APR02 E712334-4 002884 P01/7700 0.00-0208945.6
3. Full name, address and postcode of the or of each applicant (underline all surnames)	The Queen's University of Belfast University Road Belfast BT7 1NN Northern Ireland		
Patents ADP number (if you know it)			
If the applicant is a corporate body, give the country/state of its incorporation	889675001		
4. Title of the invention	"Vascular Impedance Measurement Apparatus"		
5. Name of your agent (if you have one)	Murgitroyd & Company		
"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)	Scotland House 165-169 Scotland Street GLASGOW G5 8PL		
Patents ADP number (if you know it)	1198013		
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I/We request the grant of a patent on the basis of this application

Signature *Murgitroyd & Co.*
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Date
18 April 2002

2. Name and daytime telephone number of
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1 Vascular Impedance Measurement Apparatus

2

3

4 **Introduction**

5 The present invention relates to apparatus for
6 measuring vascular impedance.

7

8 The complications of cardiovascular disease
9 represent the leading cause of morbid and mortal
10 events in Western society. At present, diagnostic
11 procedures are designed to assess the extent and
12 severity of blood vessel damage when symptoms
13 present or with the occurrence of vascular events.
14 The diagnostic challenge is to detect abnormal
15 structure and function in the vascular system at an
16 early pre-clinical stage. The ability to detect and
17 monitor sub-clinical arterial damage has the
18 potential to refine cardiovascular risk
19 stratification and enable early intervention to
20 prevent or attenuate disease progression.

21

1 Traditionally, the arterial circulation has been
2 considered a steady-flow system characterised by
3 mean arterial pressure that represents the product
4 of cardiac output and total peripheral resistance.

5
6 The pulsatile component of pressure is determined by
7 the pattern of left ventricular ejection and the
8 stroke volume. The compliance characteristics of the
9 arterial circulation has been largely ignored in
10 prior haemodynamic studies.

11
12 The importance of assessing arterial wall integrity
13 has been highlighted by studies demonstrating that a
14 reduction in the pulsatile function or compliance
15 characteristics of large arteries represents a
16 powerful independent risk factor for future
17 cardiovascular events. Accumulating evidence
18 suggests that abnormalities in the pulsatile
19 characteristics of arteries occur early in disease
20 processes associated with increased cardiovascular
21 risk. Importantly, impaired pulsatile arterial
22 function is recognised as an independent predictor
23 of risk for vascular events in patients with various
24 disease states including coronary heart disease,
25 congestive heart failure, hypertension and diabetes
26 mellitus.

27
28 Studies relating outcome to abnormalities in
29 pulsatile function have focused on large arteries,
30 although analysis of arterial pressure pulse
31 waveforms suggest that the earliest abnormalities in

1 arterial structure and function resides in the
2 microcirculation.

3

4 The study of this section of the vasculature has
5 been hindered by the lack of a non-invasive,
6 reproducible and repeatable technique capable of
7 assessing the compliance characteristics or
8 pulsatile function of small arteries and arterioles.

9

10 Physiologically, the impedance load or opposition to
11 flow presented by the circulation is measured
12 invasively by analysing the altered pressure/flow
13 relationships and pulse contour parameters produced
14 through the effects of disease on the structural and
15 functional components of the arterial system. Input
16 impedance relates simultaneously recorded pressure
17 and flow waveforms under specific mathematical
18 conditions. The haemodynamic properties of the
19 system can be quantified as the impedance concept
20 permits the heart and arteries to be considered
21 separately and their interaction understood as a
22 function of pump and load properties. As pressure
23 and flow waves are periodic and continuous, Fourier
24 series methods can be used to generate the impedance
25 function. The modulus at each harmonic in the
26 Fourier series is the ratio of the pressure modulus
27 to the flow modulus at that harmonic and the phase
28 at each harmonic is the difference between pressure
29 phase and flow phase at the same harmonic. As the
30 impedance of a vascular bed varies with frequency,
31 complete specification of pulsatile pressure and

1 flow relationships takes the form of the spectrum of
2 moduli and phase angles versus frequency⁵.

3
4 Characteristic impedance (the inverse of arterial
5 compliance) defines the relationship between
6 pressure and flow in an artery or arterial network
7 when pressure and flow waves are not influenced by
8 wave reflections. These conditions do not exist in
9 the arterial system and the input impedance values
10 oscillate around the characteristic impedance value
11 because of wave reflection. Wave reflections are
12 known to exert their greatest influence on impedance
13 moduli at low frequencies. For higher frequencies,
14 the input impedance approaches the characteristic
15 impedance which has been estimated in prior
16 haemodynamic studies as the arithmetic mean of input
17 impedance moduli above 2-4 Hz.

18
19 In the prior art, detailed studies of arterial
20 pressure and flow are only possible through the use
21 of invasive techniques. Such techniques cannot be
22 used to monitor changes in the circulatory system of
23 a patient over time because of the dangers to health
24 posed by these techniques.

25 26 **Statements of Invention**

27
28 In accordance with a first aspect of the present
29 invention there is provided apparatus for the
30 measurement of vascular impedance of the ocular
31 micro circulation *in vivo*, the apparatus comprising
32 intra-ocular pressure measurement means, from which

1 a pressure pulse waveform is calculable and blood
2 velocity profile measurement means for measuring the
3 linear blood flow velocity in the retrobulbar
4 circulation, means for calculating the vascular
5 impedance modulus from the pressure pulse waveform
6 and the linear blood flow velocity .

7
8 Preferably the arterial pulse waveform measurement
9 means measures the maximum and minimum pressure
10 values of the pulse profile to calculate a mean
11 intra-ocular pressure.

12
13 Preferably, an ocular pneumotonometer is used to
14 measure intra-ocular pressure.

15
16 Preferably the blood velocity profile measurement
17 means is an ultrasound device.

18
19 Preferably the ultrasound device is a doppler
20 ultrasound imager.

21
22 Preferably the change in the pulsatile intra-ocular
23 pressure waveform and the linear blood flow velocity
24 are measured sequentially.

25
26 Preferably, the means for calculating the vascular
27 impedance modulus comprises obtaining the fourier
28 transform of the intra-ocular pressure pulse
29 waveform and the linear blood flow velocity and
30 dividing the transformed values of the pulsatile
31 change in the intra-ocular pressure pulse by the
32 transformed retrobulbar blood flow velocity.

1

2 Preferably the pulsatile change in intra-ocular
3 pressure has a phase associated therewith.

4

5 Preferably the intra-ocular blood velocity has a
6 phase associated therewith.

7

8 In accordance with a second aspect of the present
9 invention there is provided a method for the
10 measurement of vascular impedance of the ocular
11 micro circulation *in vivo*, the method comprising the
12 steps of: measuring the intra-ocular pressure pulse
13 waveform of the ocular network;
14 measuring the linear blood flow velocity in the
15 retrobulbar circulation; and
16 calculating the vascular impedance modulus from the
17 intra ocular pressure pulse waveform and the linear
18 blood flow velocity waveform.

19

20 Preferably, the change in the pulsatile intra-ocular
21 pressure waveform and the linear blood flow velocity
22 are measured sequentially.

23

24 **Specific Description**

25

26 The invention will now be described by way of
27 example only with reference to the accompanying
28 drawings in which:

29

30 Fig.1 is a diagram of an eye having means for
31 measuring the intra-ocular pressure using the

1 principle of applanation tonometry at the front of
2 the eye;

3

4 Fig.2 is a diagram of an eye having means for
5 measuring the linear flow velocity by interrogating
6 the retrobulbar circulation from the front of the
7 eye;

8

9 Fig.3 is a graph of the periodic pressure signal as
10 measured using the present invention plotted against
11 time;

12

13 Fig.4 is a graph of the periodic velocity signal as
14 measured using the present invention plotted against
15 time;

16

17 Fig.5 is a graph of impedance modulus plotted
18 against frequency; and

19

20 Fig.6 is a graph of phase plotted against frequency.

21

22 Figs. 1 and 2 show a first embodiment of the present
23 invention. Figs.1 and 2 are diagrams showing some
24 features of the human eye 1. These include the
25 optic nerve 3, the ophthalmic artery 5, a bolus of
26 blood contained in the ophthalmic artery 5
27 positioned outside the ocular vascular network 9.
28 The vein 11 is also shown.

29

30 Fig.1 also shows the means for measuring the intra-
31 ocular pressure 13; provided, in this example by a
32 tonometer system applanated to the cornea 23.

1
2 Fig.2 shows means for measuring the linear blood
3 flow velocity in the retrobulbar circulation 17,
4 connected to the front of the eye. This is an
5 ultrasonic device that is placed on the eyelid
6 19, the eyelid 19 being covered with a gel 21 to
7 ensure that the ultrasound device is properly
8 coupled to the eye 1. This device measures the
9 linear velocity of the bolus of blood 7 in the
10 ophthalmic artery 5.

11
12 In use, the tonometer system 13 employs continuous
13 airflow pneumotonometry with a probe 15 applanated
14 on the cornea to record intraocular pressure using a
15 pneumatic sensor. The device samples at 200 Hz with
16 a resolution of 0.01 mmHg and the signals are
17 acquired over a 20 second period. Pulsatile
18 variation of intraocular pressure results from
19 pressure oscillations generated by cardiac
20 contraction altering the distending pressure in the
21 vessel walls. Compliance of an artery, or an entire
22 arterial bed, describes the ability to store a
23 varying amount of blood. Changes in volume within
24 the ocular vascular bed will produce an equal change
25 in volume. The pulsatile ocular waveforms are
26 recorded after administration of oxybuprocaine 0.4%
27 drops to anaesthetise the cornea.

28
29 The variation in intra-ocular pressure as a function
30 of time reflects the introduction of the bolus of
31 blood 7 into the ocular vascular network 9. The

1 ocular vascular network 9 expands to accommodate the
2 additional volume of blood.

3

4 As the intra-ocular fluids are incompressible, the
5 intra-ocular pressure response to the volume change
6 will depend of the viscoelastic properties of the
7 vessel network and the ocular rigidity. The
8 mechanical properties and distending pressures will
9 vary at different sites in the ocular vascular
10 network 9 and it is the composite effect of these
11 influences that determine the intra-ocular pressure
12 waveform morphology. Whilst the rigidity of the
13 ocular coat can vary between individuals, the half-
14 life of the collagen and elastin components are
15 measured in years. Consequently, the characteristics
16 of these boundary structures would not be expected
17 to change significantly within an individual over a
18 period of weeks or months. Therefore changes
19 recorded in the intra-ocular pressure pulse waveform
20 will be reflective of alteration in the viscoelastic
21 properties of the ocular microcirculatory bed.

22

23 The present invention uses the directly recorded
24 change in intra-ocular pressure in its analysis and
25 not the generated flow output measurements from the
26 device that relate pressure change to volume change
27 within the eye. The pulsatility of the intra-ocular
28 pressure is dependent on the pulsatile inflow and
29 distension of the vessels which is related to the
30 viscoelastic properties of the ocular circulation.
31 Scleral rigidity may limit the frequency of pressure

1 fluctuations but does not cause variation in
2 pressure.

3

4 In the example shown in Fig.2, a colour doppler
5 ultrasound imager 17 is used to examine the blood
6 velocity waveform in the retrobulbar ocular
7 circulation. This technique employs simultaneous B-
8 scan and doppler imaging to allow location and
9 identification of blood vessels. The sample volume
10 defined by the imager 17 is placed over a vessel of
11 interest, in this case, the bolus of blood 7 and the
12 frequency shifts received are assembled into a
13 spectral waveform. The spectral waveform represents
14 the cumulative frequency shifts present and can be
15 displayed as a time-velocity waveform.

16

17 In use, alternate measurements of the arterial pulse
18 waveform and blood velocity profile are taken.
19 The shape of the linear velocity flow waveform,
20 recorded in the retrobulbar circulation , is
21 determined by and is critically dependent on changes
22 in total cross-sectional area of the ocular vascular
23 network.

24

25 Like pressure, flow will also vary at different
26 sites in the ocular vascular network 9 and the
27 velocity waveform morphology therefore reflects the
28 status of the entire ocular vascular network 9. In
29 essence, the flow velocity waveform derived from the
30 retrobulbar circulation and the intra-ocular
31 pressure waveform reflect the sum total of the

1 various calibre and pressure changes throughout the
2 ocular vascular bed.
3 Measured over time, changes in the linear flow
4 waveform can provide information on changes in the
5 ability of the ocular vascular network to expand
6 during the cardiac cycle. Such information can lead
7 to early diagnosis and subsequent early treatment of
8 disease.

9
10 The present invention uses linear velocity of flow
11 in calculating the vascular impedance of the
12 microcirculation as changes in velocity of flow are
13 determined by changes in the total cross-sectional
14 area of the ocular vascular network 9. Furthermore,
15 the use of linear velocity of flow permits
16 comparisons of impedance moduli derived from
17 different arteries and in the same artery under
18 varying conditions. This comparison cannot be
19 validly made using volume flow measurements.

20
21 Typical examples of intraocular pressure and
22 velocity profiles (obtained from the ophthalmic
23 artery) are shown in Figures 3 and 4.

24
25 Fig. 3 is a graph of pressure plotted with respect
26 to time. The figure shows the periodicity of the
27 pressure fluctuation. The cardiac cycle can be
28 identified from the period of the pressure
29 fluctuation as being approximately 0.9 s.

30

31 Fig. 4 is a graph of linear blood velocity plotted
32 with respect to time. The figure shows the

1 periodicity of linear velocity fluctuation. The
 2 cardiac cycle can be identified from the period of
 3 the linear velocity fluctuation as being
 4 approximately 0.9s.

5
 6 The sites of data acquisition enable the recording
 7 of pressure and linear velocity waveforms that
 8 provide information about the entire ocular vascular
 9 network and not merely single vessel in the network.
 10 Measurements are obtained sequentially using the
 11 tangent method to align pressure and velocity
 12 waveforms. This technique is employed to ensure
 13 effective alignment of waveforms for analysis. The
 14 signals may also be gated to an ECG. Other known
 15 methods may also be employed.

16
 17 As seen in Figures 3 and 4, the velocity and
 18 pressure signals are periodic and time dependent and
 19 can thus be represented in the frequency domain by
 20 obtaining their Fourier transform: $P(\omega) = FT [P(t)]$
 21 and $V(\omega) = FT[V(t)]$ where FT represents Fourier
 22 transformation. In addition, each frequency
 23 component of pressure and velocity will have its own
 24 associated phase (ϕ_p pressure phase, ϕ_v velocity
 25 phase). The frequency dependent impedance modulus
 26 and phase can be determined from: $Z(\omega) = P(\omega)/V(\omega)$
 27 and $\phi(\omega) = \phi_p(\omega) - \phi_v(\omega)$.

28
 29 Figures 5 and 6 show typical plots of $Z(\omega)$ and $\phi(\omega)$
 30 for a normal subject.

31

1 The flow and first derivative of pressure occur at
2 similar time points. As pressure and flow are
3 obtained sequentially the first derivative of the
4 pressure waveform is aligned to the flow waveform.
5 A tangent to end diastole and a tangent to the
6 initial upstroke in pressure wall intersect at the
7 "foot" of the waveform. This point is aligned with
8 the same point on the flow waveform.

9
10 Frequency domain analysis provides information about
11 steady-state (resistance) and pulsatile function
12 (characteristic impedance) of the ocular
13 circulation. In Fig. 5, the steady state resistance
14 is shown in area A and the characteristic impedance
15 in area B. These signals are stored in digital form
16 and the digitised signals are amenable to analysis
17 in the time domain with the application of
18 mathematical models to interpret waveshape changes
19 in relation to the mechanical properties of the
20 ocular circulatory bed.

21
22 The present invention is highly advantageous with
23 respect to the prior art because it provides a non-
24 invasive method and apparatus for measuring vascular
25 impedance and in particular, through interrogation
26 of the wave shape, of the linear velocity profile of
27 the blood bolus in the retrobulbar circulation.

28 Previously, invasive techniques had only been
29 thought capable of providing information on the
30 linear velocity profile. Such techniques are

31 expensive and cannot be used to obtain repeat
32 results over a period of time for the same subject.

1 The present invention therefore allows a physician
2 to monitor changes in the microcirculation of the
3 eye and to extrapolate the data to make clinical
4 judgements in various disease states associated with
5 an increase in cardiovascular events.

6
7 The present invention is applicable in a number of
8 areas of clinical research. Some examples are given
9 below.

10
11 It has been recognised for many years that
12 characteristic changes in the arterial pressure
13 pulse contour occur in many disease states and with
14 physiological and pharmacological interventions.
15 Alteration in arterial waveform morphology typically
16 involves a steepening of the diastolic decay and a
17 diminution in the amplitude and duration of the
18 oscillatory waveform that distorts the proximal part
19 of diastole from a pure monoexponential. The
20 oscillatory diastolic waveform arises from wave
21 reflection and damped resonance occurring in the
22 arterial tree with the major sites of reflected
23 waves originating in smaller arteries and
24 arterioles. Loss of the oscillatory diastolic
25 waveform is recognised as an early marker of altered
26 vessel wall properties that identifies impaired
27 pulsatile function of arteries as it can be found in
28 patients at increased cardiovascular risk without
29 alteration in total peripheral resistance. This has
30 been demonstrated in patients with diabetes mellitus
31 and cigarette smokers. Whilst the microvascular
32 changes associated with diabetes are well

1 recognised, the structural changes that are commonly
2 found in the arterioles of smokers and rarely in
3 non-smokers, are less well appreciated. These
4 microvascular abnormalities may account for the
5 common occurrence of microinfarcts found in
6 association with diabetes and cigarette smoking that
7 have hitherto gone unrecognised.

8

9 Analysis of the arterial pressure pulse waveform can
10 also be useful in identifying the haemodynamic
11 action of drug therapy not detected by the
12 traditional measurement of peripheral resistance.

13

14 Improvements and modifications may be incorporated herein
15 without deviating from the scope of the invention.

FIG. 1

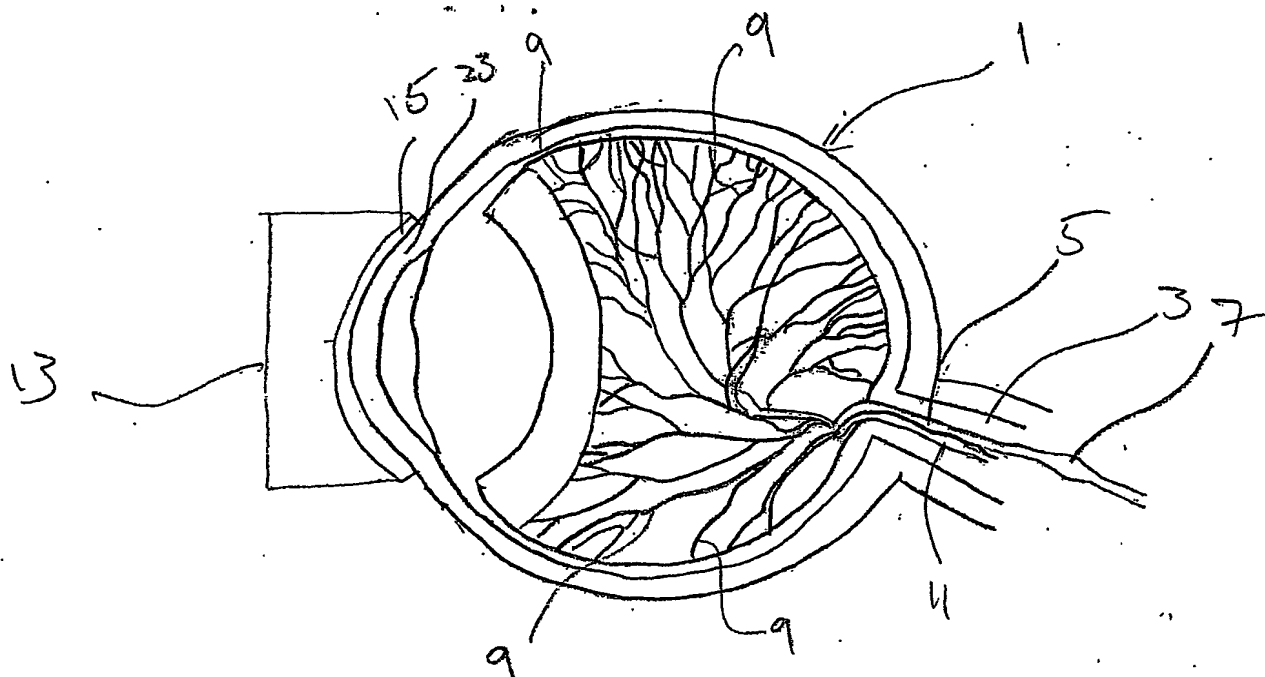
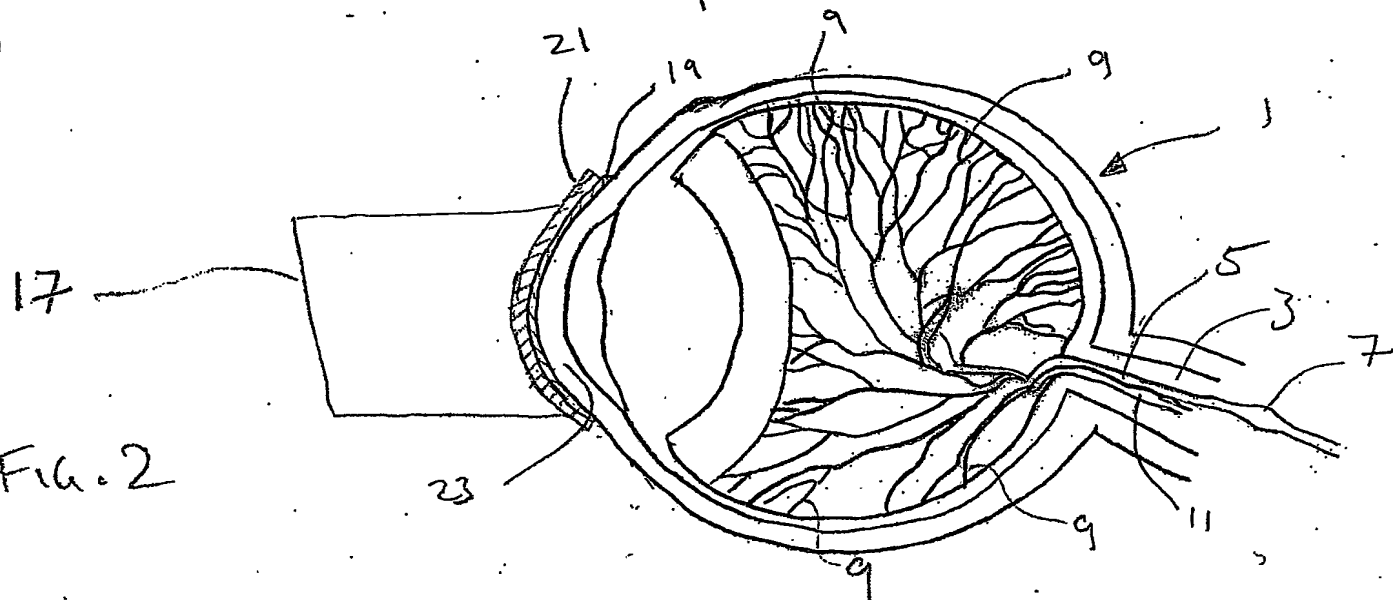


FIG. 2



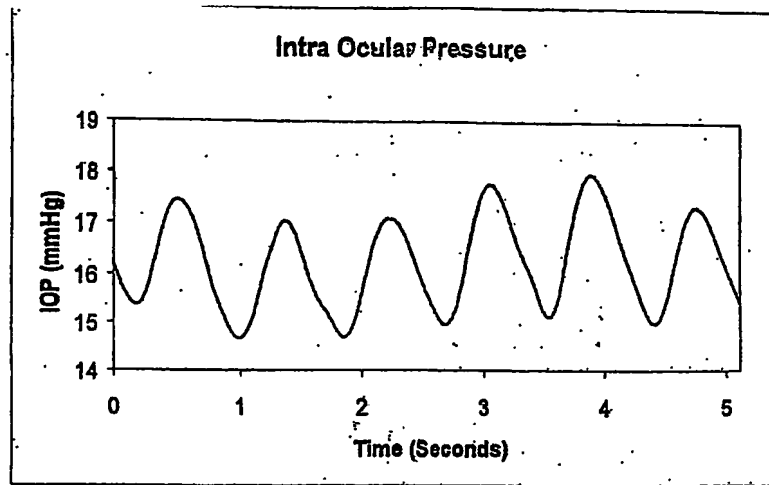


FIG-3

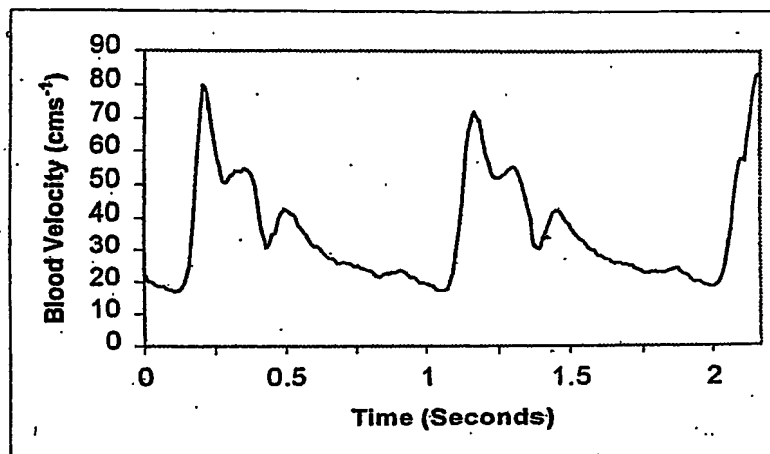


FIG. 4

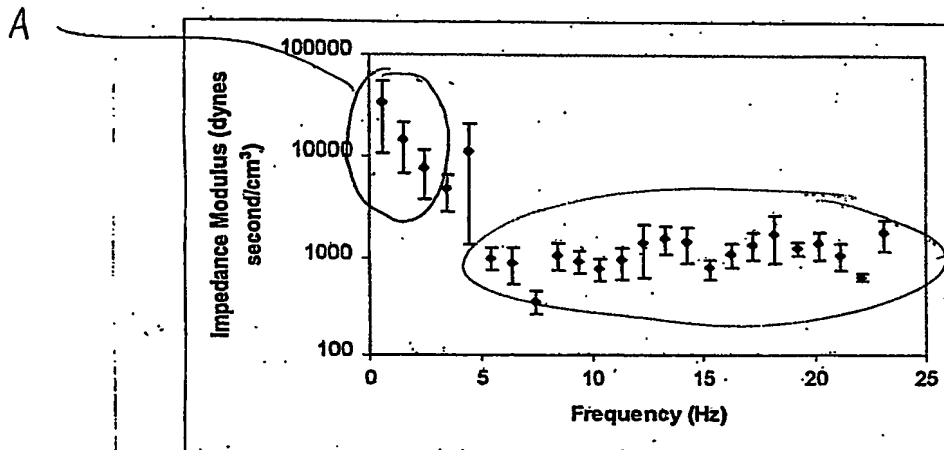


FIG-5

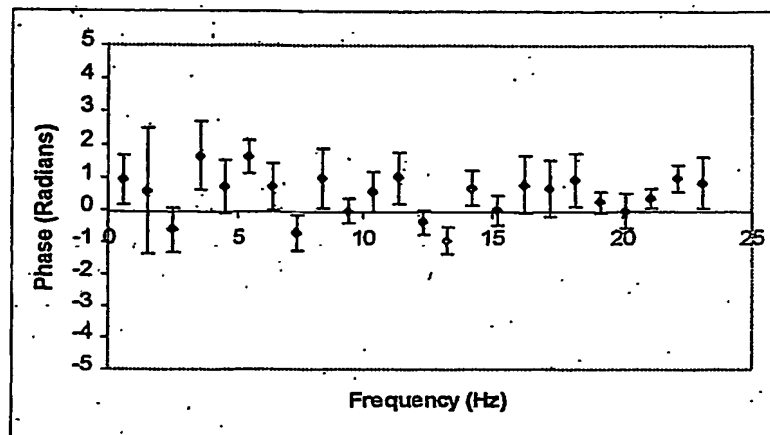


FIG. 6

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